REMARKS

Claims 43-48, 50, 59-60 and 62-80 were pending in the application. Claims 43, 45 and 78-80 have been canceled without prejudice and claims 44, 48, 50, 59-60 and 62-77 have been amended. New claims 81-285 have been added. Accordingly, claims 44, 46-48, 50, 59-60, 62-77 and 81-285 will remain pending upon entry of the instant amendment.

Support for the claim amendments and new claims can be found in the original claims and specification as filed. No new matter has been added by way of these amendments.

The foregoing claim amendments and cancellations should in no way be construed as an acquiescence to any of the Examiner's rejections and were made solely to expedite prosecution of the present application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Acknowledgements

Applicants gratefully acknowledge that claims 46-48, 62, 67 and 70-80 have been indicated as allowable by the Examiner. Applicants further gratefully acknowledge that the Examiner has expanded the search of the elected species of breast cancer to include colon and pancreatic cancers, and that the species restriction between breast, colon and pancreatic cancers is thereby withdrawn. Applicants understand that the species restriction as it applies to other cancers recited in the claims, *i.e.*, testicular, lung, ovary, bladder, uterine, cervical and stomach cancer, is still valid.

Applicants gratefully acknowledge the withdrawal of the objection to claims 46-48, 62, 70 and 73-78 for reciting non-elected inventions. Applicants also gratefully acknowledge the withdrawal of the following rejections: (1) the rejection of claim 43 under 35 USC § 112, second paragraph, as being indefinite; (2) the rejection of claims 46, 47, 62, 70, 74 and 78 under 35 USC § 112, second paragraph, as being indefinite; (3) the rejection of claim 67 under 35 USC § 112, second paragraph, as being indefinite; (4) the rejection of claim 76 under 35 USC § 112, second paragraph, as being indefinite; (5) the rejection of claims 48, 71, 72 and 77 under 35 USC § 112, first paragraph, for lack of enablement; (6) the rejection of claim

78 under 35 USC § 112, first paragraph, for lack of written description; and (7) the rejection of claims 43, 44-47, 50, 58-60, 62-70, 74, 76, 78 under 35 USC § 103(a) as being obvious over Qi *et al.* in view of Meissner and Coleman, Williams *et al.*, Dan *et al.* and Chari *et al.*.

Objections to the Claims

The Examiner has maintained the objection to claim 50 as reciting non-elected inventions. Applicants respectfully submit that, as acknowledged by the Examiner, the species of "breast tumor cells" has been elected for search purposes only. It is Applicants' understanding that the search will be extended to the remaining, unexamined species of testicular, lung, ovary, bladder, uterine, cervical and stomach cancers upon a finding of allowability. Accordingly, the claims have not been amended so as to be directed solely to the elected species at this time.

Rejection of Claims 43-45, 50, 59 and 63-65 Under 35 USC § 102(b).

Claims 43-45, 50, 59 and 63-65 have been rejected under 35 USC § 102(b) as being anticipated by Meissner and Coleman (U.S. Patent 5,981,215). The Examiner relies on Meissner and Coleman for allegedly teaching "human Criptin Growth Factor polypeptide (CGF) (SEQ ID NO:7, that is 100% identical to SEQ ID NO:1 of the instant application..." The Examiner further states that Meissner and Coleman teach "antagonist against such polypeptides, wherein the potential CGF antagonist compounds includes antibodies." In response to Applicants' arguments set forth in the Amendment and Response filed August 16, 2006, the Examiner states that

> ***[s]ince the instant claims are not drawn to any particular sequence of Cripto, it is irrelevant what CGF polypeptide Meissner and Coleman performed their experiments with***. Meissner and Coleman teach that the ***Cripto antibodies*** can be employed in inhibition of tumor growth (which indicates that the proliferation of tumor cells can be inhibited), that the antibody can be monoclonal and a composition with a pharmaceutically acceptable carrier, in addition to suggesting that ***anti-Cripto antibodies*** can be used for human administration."

Applicants respectfully traverse this rejection based on the following reasons.

At the outset, Applicants wish to reiterate that, contrary to the Examiner's assertion, ***Meissner and Coleman disclose the sequence of "Criptin Growth Factor polypeptide" (CGF) in SEQ ID NO:2 of the reference,*** and ***not in SEQ ID NO:7*** (see column 1, lines 34-38 and column 2, lines 31-41 of Meissner and Coleman). The sequence of SEQ ID NO: 2 in the Meissner and Coleman reference encoding "Criptin Growth Factor" displays only 21.6% identity to "Cripto Growth Factor" or Cripto-1 (SEQ ID NO: 1 of the instant application) over its full length and is 52% identical to Cripto in a 69 amino acid overlap. The sequence of ***Cripto-1*** is presented in ***SEQ ID NO: 7*** of the Meissner and Coleman reference, and indeed, an alignment of the ***distinct CGF and Cripto-1 sequences*** is presented in Figure 2 of Meissner and Coleman (see column 2, lines 38-41). The entire Meissner and Coleman reference is directed to CGF, and not to Cripto-1.

The instant application defines the term "Cripto" at page 17, lines 10-26 of the specification, as follows:

> As used herein, ***Cripto includes the CR-1 Cripto protein, the CR-3 Cripto protein, and fragments thereof.*** Such fragments may be entire domains, such as the extracellular or intracellular domains, the EGF-like domain, the cys-rich domain, the receptor binding domain, and the like. Such fragments may also include contiguous and noncontiguous epitopes in any domain of the Cripto protein.
>
> ***The 188 amino acid sequence for CR-1 is as follows [SEQ ID NO: 1]:***
>
> MDCRKMARFSYSVIWIMAISKVFELGLVAGLGHQEFARPSRGYLA
> FRDDSIWPQEEPAIRPRSSQRVPPMGIQHSKELNRTCCLNGGTCML
> GSFCACPPSFYGRNCEHDVRKENCGSVPHDTWLPKKCSLCKCWH
> GQLRCFPQAFLPGCDGLVMDEHLVASRTPELPPSARTTTFMLVGIC
> LSIQSYY
>
> ***The 188 amino acid sequence for CR-3 is as follows [SEQ ID NO: 2]:***
>
> MDCRKMVRFSYSVIWIMAISKAFELGLVAGLGHQEFARPSRGDLA
> FRDDSIWPQEEPAIRPRSSQRVLPMGIQHSKELNRTCCLNGGTCML
> ESFCACPPSFYGRNCEHDVRKENCGSVPHDTWLPKKCSLCKCWH
> GQLRCFPQAFLPGCDGLVMDEHLVASRTPELPPSARTTTFMLAGIC
> LSIQSYY

Thus, the teachings of Meissner and Coleman, which are directed to the CGF polypeptide, fail to anticipate the instant claims directed to methods of inhibiting

tumor cell proliferation or treating a subject using monoclonal antibodies to ***Cripto, e.g., Cripto-1 or Cripto-3***.

In view of the foregoing, although Meissner and Coleman disclose making antagonists of ***CGF***, the reference does not teach or suggest methods of inhibiting tumor cell proliferation or treating a subject using antagonists of ***Cripto***, let alone ***monoclonal antibodies to Cripto*** as required by the presently pending claims. It appears that the Examiner is equating the polypeptide of Cripto with the polypeptide of CGF. Applicants respectfully submit that Cripto is a specific polypeptide that is a completely distinct molecule from the polypeptide of CGF (as discussed above). Therefore, Meissner and Coleman fail to teach or suggest the use of monoclonal antibodies that bind to ***Cripto*** to inhibit tumor cell proliferation or to treat a subject as required by the pending claims.

Notwithstanding the foregoing, in the interest of expediting prosecution and in no way acquiescing to the Examiner's allegations, claims 43 and 45 have been canceled, thereby rendering the rejection moot as it pertains to these claims. Further, claims 44, 50, 59 and 63-65 have been amended such that these claims now depend from claims which were indicated by the Examiner as allowed, and/or depend from claims which encompass all of the limitations of the allowed claims. Applicants submit that these claim amendments render the rejection of the claims as being anticipated by Meissner and Coleman moot.

Rejection of Claims 43-45, 50, 59, 60, 63-66, 68 and 69 Under 35 USC § 103(a).

Claims 43-45, 50, 59, 60, 63-66, 68 and 69 have been rejected under 35 USC § 103(a) as being unpatentable over Meissner and Coleman (U.S. 5,981,215), in view of Queen *et al.* (U.S. 5,530,101), in view of Dan *et al* (U.S. 6,207,153) and further in view of Chari *et al.* (U.S. 6,333,410). This rejection is respectfully traversed.

The Examiner relies on Meissner and Coleman for the reasons discussed above. The Examiner acknowledges that Meissner and Coleman "does not teach the human antibody, and the conjugation of antibody to a chemotherapeutic agent, wherein the therapeutic agent is selected from the group consisting of a tumor-activated prodrug, a radionuclide and a toxin, and further wherein the agent is [a] maytansinoid."

The Examiner further relies upon Queen *et al.* for allegedly teaching "human and humanized antibodies," as well as "antibody conjugation to a variety of cytotoxic agents including radioisotopes, chemotherapeutic drugs, toxins" and "pharmaceutical compositions comprising such antibodies." The Examiner further relies on Dan *et al.* as allegedly teaching "a monoclonal antibody H11 and antigen binding fragments that specifically bind to the antigen recognized by H11, the C-antigen, which is found specifically on neoplastic cells and not on normal cells." Finally, the Examiner relies on the Chari *et al.* as allegedly teaching "antibody drug-conjugates utilizing Maytansinoids as a conjugate."

The Examiner contends that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced the claimed method of modulating growth of tumor cells in vivo in a subject comprising the step of administering to the subject an effective amount of an antibody that binds Cripto and a pharmaceutically acceptable carrier. The Examiner states:

> One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the antibodies to cripto-1 for therapeutic advantages, based on the teachings of Meissner and Coleman because Meissner and Colemen teach... human Criptin Growth Factor polypeptide (CGF) (SEQ ID NO:7 that is 100% identical to SEQ ID NO:1 of the instant application...) in addition to teaching antibodies against such polypeptides, and their use as a therapeutic to treat and/or prevent neoplasia such as tumors, and, thereby competitively inhibiting the action of CGF, wherein the antibody may be employed to inhibit tumor growth, directly or indirectly.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some ***suggestion or motivation***, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a ***reasonable expectation of success*** at the time the invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143.

Applicants traverse the rejection. As discussed above with respect to the rejection of the claims under 35 USC § 102(b), Meissner and Coleman disclose the use of antagonists against human ***Criptin Growth Factor polypeptide*** (***CGF***). The

sequence of ***CGF*** is presented in ***SEQ ID NO:2*** of the Meissner and Coleman reference, and ***not in SEQ ID NO:7, as stated by the Examiner***. (See column 1, lines 34-38 and column 2, lines 31-41 of Meissner and Coleman). The sequence of SEQ ID NO: 2 in the Meissner and Coleman reference encoding "Criptin Growth Factor" displays only 21.6% identity to Cripto (SEQ ID NO: 1 of the instant application and also presented in SEQ ID NO: 7 of the Meissner and Coleman reference) over its full length and is 52% identical to Cripto in a 69 amino acid overlap. An alignment of the CGF and Cripto sequences is shown in Figure 2 of the reference. (See column 2, lines 38-41). Although Meissner and Coleman disclose making antagonists of CGF, the reference does not teach or suggest methods of inhibiting tumor cell proliferation or treating a subject using antagonists of ***Cripto***, let alone ***monoclonal antibodies to Cripto*** as required by the presently pending claims. Therefore, the primary reference cited by the Examiner fails to teach or suggest the use of monoclonal antibodies that bind to Cripto to inhibit tumor cell proliferation or to treat a subject as required by the pending claims.

The Dan *et al.* reference fails to make up for the deficiencies in the primary reference. The Dan *et al.* reference discloses the monoclonal antibody H11 and antigen binding fragments that specifically bind to the antigen recognized by H11, the C antigen. The reference fails to teach or suggest the use of an anti-Cripto antibody to inhibit proliferation of tumor cells or to treat tumors.

The Chari *et al.* reference also fails to make up for the deficiencies in the primary reference. The Chari et al. reference discloses antibody drug-conjugates utilizing maytansinoids as a conjugate. The reference fails to teach or suggest the use of an anti-Cripto antibody to inhibit proliferation of tumor cells or to treat tumors.

Accordingly, neither the primary nor the secondary references applied by the Examiner (*i.e.,* the Meissner and Coleman, the Dan *et al.*, and the Chari *et al.* reference) teach or suggest antibodies to Cripto, let alone using such antibodies in the presently claimed methods. Applicants submit that the Examiner has failed to point to any teaching in the Meissner and Coleman, Dan *et al.* and Chari *et al.* references that would compel one of ordinary skill in the art to make the claimed invention. The prior art must suggest "to those of ordinary skill in the art that they ***should*** make the claimed composition or device, or carry out the claimed process" and "***[b]oth the suggestion*** and the ***reasonable expectation of success*** must be founded in ***the prior***

art, not in the applicant's disclosure." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Notwithstanding the foregoing, in the interest of expediting prosecution and in no way acquiescing to the Examiner's allegations, claims 43 and 45 have been canceled, thereby rendering the rejection moot as it pertains to these claims. Further, claims 44, 50, 59, 60, 63-66, 68 and 69 have been amended such that these claims now depend from claims which were indicated by the Examiner as allowed, and/or depend from claims which encompass all of the limitations of the allowed claims. Applicants submit that these claim amendments render the rejection of the claims as being obvious over Meissner and Coleman in view of Dan *et al.* and Chari *et al.* moot.

Rejection of Claims 43-48, 50, 58-60 and 62-78 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting.

Claims 43-48, 50, 58-60, and 62-78 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 88-104 of copending Application No. 10/945,853.

Applicants respectfully acknowledge the provisional rejection of these claims. However, since claims 88-104 of the '853 application are not presently patented or indicated as allowed, Applicants will address this rejection in the co-pending application and consider filing a terminal disclaimer at that time.

CONCLUSION

If a telephone conversation with the Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at 617-227-7400.

Dated: **May 1, 2007**

Respectfully submitted,

By _____

Megan E. Williams
Registration No. 43,270
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent for Applicants